PATENT

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Applicant:	Wayne R. Danter *et al.*	:	Paper No.:
Serial No.	10/522,944	:	Group Art Unit: 1624
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For:	**Protein Tyrosine Kinase Inhibitors**		

DECLARATION UNDER 37 C.F.R. 1.132

Box Fee Amendment
Commissioner for Patents
Washington, DC 20231

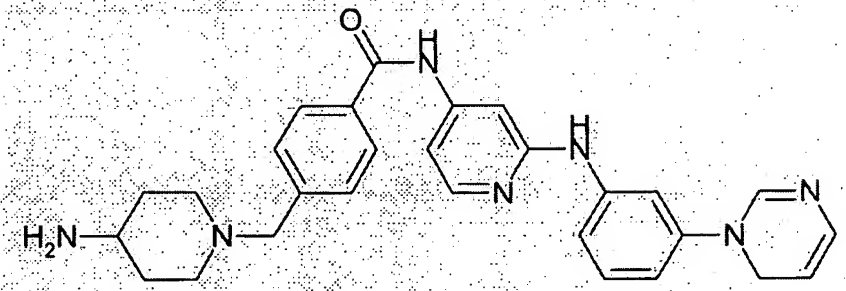
I, Dr. Wayne R. Danter, do hereby declare and say as follows:

1. I obtained an Doctorate in Medicine (MD) from the University of Western Ontario in London, Canada, in **1978**. After completing a residency training program in Internal Medicine and post doctoral research training in Clinical Pharmacology, I became an Assistant Professor in the Department of Medicine at the University of Western Ontario in July, **1987**. I was promoted to Associate Professor of Medicine in **1997**. In addition to teaching, my clinical focus was in general Cardiology, Cardiovascular Diseases associated with HIV, and Cardiovascular Risk Management. I conducted my research into the application of Artificial Intelligence (AI) models to (1) disease diagnosis (2) therapeutic outcome prediction and (3) computational Structure Activity Relationships (SAR) beginning in 1988. My primary research focus was on predicting specific relationships between molecular structure and biological activity in order to discover potential new treatments for cancers and HIV. While at the University of Western Ontario, I authored several peer reviewed journal publications and delivered a number of international conference presentations in this field. My research eventually resulted in a proprietary process called CHEMSAS™ that is used to predict specific biological activities of therapeutic candidates based on their chemical structure. CHEMSAS is based on a very straightforward process. The traditional drug discovery process was first

decomposed into its most basic elements. A computer simulation was then developed and validated for each individual basic element. Finally the individual validated computational elements were reassembled in to a multi-step process. CHEMSAS is currently able to produce a detailed molecular profile by making predictions about targeted efficacy, physical chemical and general ADMET properties. This computational molecular profile can be combined with human expertise to select molecules for synthesis, patenting and preclinical development. Although not extensively published, this process has been used in developing a number of candidate therapeutic molecules which are the subject of at least the following US patent applications: 10/531,107; 60/416,911; 10/522,944; 60/399,408; 60/884,489; 60/907,285; 12/013,079; 60/884,504; 61/081,676; 61/006,150. In **1999**, I founded Critical Outcome Technologies, Inc. (COTI) to further develop and commercialize the CHEMSAS™ process. I currently hold the positions of President, Chief Scientific Officer, and Director of COTI.

2. I am a named inventor on the above-referenced patent application and am familiar with the contents thereof.

3. The formulas of the present invention comprise, amongst other compounds, the compound of Formula III, which is indicated as COTI-003. This formula is reproduced below:



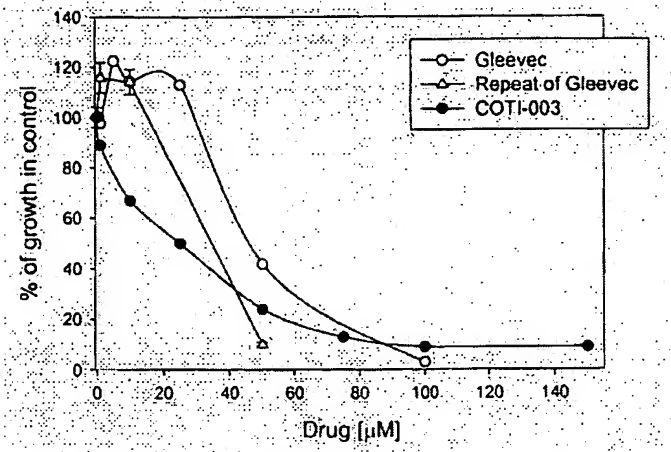
Formula III

4. As described on page 28, lines 9-22, of the description, compounds with potential tyrosine kinase activity were analyzed in a validated *in silico* assay that is based on public domain National Cancer Institute *in vitro* anti-cancer data. The molecules are first decomposed to 110 descriptors using a proprietary CHEMSAS™ algorithm. This

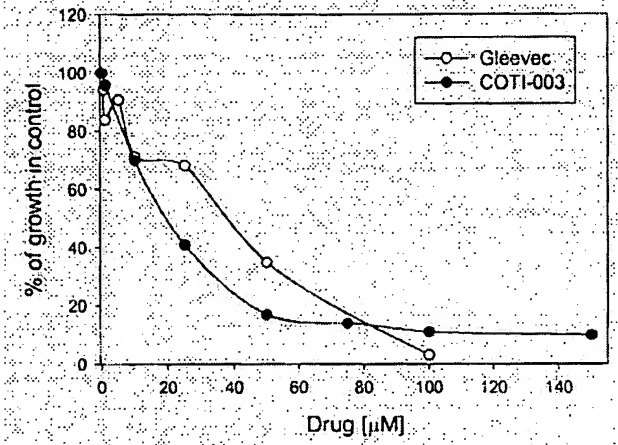
decomposition process results in a molecular data pattern of 110 variables that is then input into the *in silico* model. The output of the model is a prediction of the -Log(GI50) for the molecule(s) being analyzed against the specific cancer cell type in question. The *in silico* data found in Table 1 on page 29 of the description clearly predicts that compounds of Formula I, particularly the compound designated COTI-003, are effective at inhibiting the growth of a variety of cancer cells of different origin, including leukemias, lung cancers, colon cancers, etc.

5. Further *in vitro* data, validating the predictive value of the *in silico* data, is provided in the graphs and tables found below. This data shows the results of treatment of leukemia cells with COTI-003 or Gleevec.

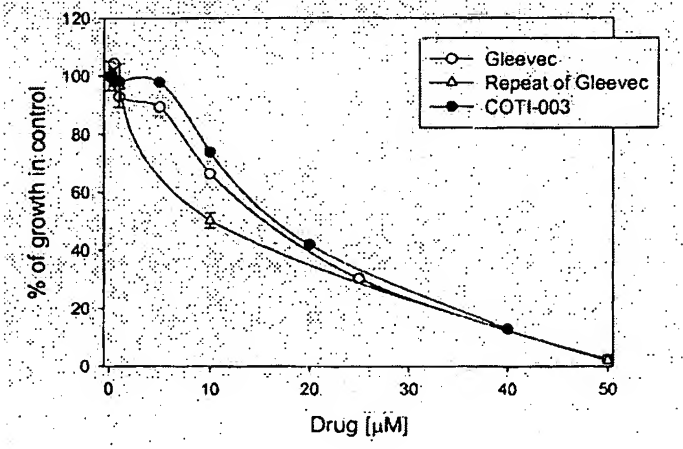
COTI-003 or Gleevec
Human HL-60 cells derived from acute promyeolocytic leukemia



COTI-003 or Gleevec
Human THP-1 cells derived from acute monocytic leukemia



COTI-003 or Gleevec
Mouse L1210 cells derived from lymphocytic leukemia



THP-1 cells, derived from acute human monocytic leukemia
Survival after exposure to Gleevec or COTI-003

COTI-003 (μM)	% survival	SE
0.0000	100.0000	1.3000
1.0000	96.0000	0.8000
10.0000	70.0000	2.2000
25.0000	41.0000	0.4000
50.0000	17.0000	0.3000
75.0000	14.0000	0.3000
100.0000	11.0000	0.1000
150.0000	10.0000	0.1000

Gleevec (μM)	% survival	SE
0.0000	100.0000	0.9000
0.5000	94.3000	1.1000
1.0000	83.9000	1.7000
5.0000	90.8000	1.0000
10.0000	71.3000	1.9000
25.0000	68.2000	0.7000
50.0000	35.0000	0.3000
100.0000	3.1000	0.0000

HL-60 cells, derived from acute human promyeolcytic leukemia
Survival after exposure to Gleevec or COTI-003

COTI-003 (μM)	% survival	SE
0.0000	100.0000	2.2
1.0000	89.0000	1.8
10.0000	67.0000	1.5
25.0000	50.0000	1.0
50.0000	24.0000	0.7
75.0000	13.0000	0.5
100.0000	9.0000	0.1
150.0000	9.0000	0.1

Gleevec (μM)	% survival	SE
0.0000	100.0000	3.1
0.5000	100.4000	2.0
1.0000	97.6000	2.6
5.0000	122.4000	5.4
10.0000	114.4000	3.2
25.0000	113.0000	4.2
50.0000	41.9000	1.6
100.0000	3.1000	0.6

L1210 cells, derived from acute mouse lymphocytic leukemia
Survival after exposure to Gleevec or COTI-003

COTI-003 (μM)	% survival	SD
0.0000	100.0000	0.0500
0.1000	100.0000	0.0100
0.5000	98.0000	0.01
1.0000	98.0000	0.01
5.0000	98.0000	0.01
10.0000	74.0000	0.03
20.0000	42.0000	0.08
40.0000	13.0000	0.01

Gleevec (μM)	% survival	SD
0.0000	100.0000	0.0600
0.5000	104.4000	0.08000
1.0000	93.0000	0.03000
5.0000	89.4000	0.04000
10.0000	66.6000	0.1100
25.0000	30.4000	0.0500
50.0000	2.5000	1.5000

6. This data further confirms the predictive value of the *in silico* data presented in Table 1 on page 29 of the description, by demonstrating *in vitro* that COTI-003 has activity against leukemia cells.

7. The K562 cell line is described on page 28 of the description as over-expressing the abnormal protein tyrosine kinase found in Chronic Myelogenous Leukemia (CML). Referring to Table 1 on page 29 of the description, COTI-003 was effective in inhibiting growth and survival of K562 leukemia cells. It is therefore reasonable to predict that COTI-003 has efficacy in the treatment of tyrosine kinase dependent cancers, such as CML.

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dr. Wayne R. Danter
London, Canada
October 14, 2008